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(57) Abstract

This invention relates to nutrient and therapeutic compositions for the treatment of cancer symptoms and conditions. Compositions of this invention contain a mixture of antioxidants, components that promote collagen maintenance and synthesis, components that regulate blood lipids, glucose and/or insulin, and lower homocysteine levels. Compositions also provide supplementation for nutrient (vitamin, mineral and cofactor) deficiencies to restore and maintain normal biochemical function. Cancer formulations, particularly those adapted for treatment of female cancers, can be combined with components that provide benefit in osteoporosis.

NUTRIENT AND THERAPEUTIC COMPOSITIONS FOR THE TREATMENT OF CANCER

FIELD OF THE INVENTION

This invention relates to nutrient compositions and to therapeutic compositions for the amelioration of cancer. Cancer-protective and cancer-therapeutic compositions of this invention include antioxidants, neovascular regulators, promoters or cofactors involved in collagen synthesis, as well as vitamins and minerals to supplement nutrient deficiencies.

BACKGROUND OF THE INVENTION

Cancerous cells exhibit certain characteristics that distinguish them from normal cells. These cells exhibit aberrant metabolism and growth, often the result of genetic damage; they exhibit proliferation due to inappropriate vascularization leading to tumor development; and they can undergo metastasis leading to the spread and recurrence of cancer.

Current cancer therapies are most often directed to the removal of cancerous tissue and the direct destruction of cancerous cells. The present invention is, in contrast, designed to utilize multi-component formulations the combined ingredients of which simultaneously interfere with a variety of factors or mechanisms that promote the generation, growth and spread of cancerous cells and tissue. More specifically the formulas of the present invention contain components which inhibit the development of cancer cells, inhibit proliferation of cancer cells and inhibit metathesis. Formulas of this invention contain additional components that promote cellular repair and the restoration of collagen matrices in tissues. Further formula ingredients are provided to restore and maintain pH balance and to stimulate the immune system. Vitamins and minerals are also included to supplement deficiencies including those that can result from cachexia induced by tumor development and growth and help restore normal biochemical function to cells and tissue. Additional formula components are included to control the level and type of blood-born lipids which may be related to increased cancer risk. The control of lipoprotein (a) is of particular importance. Further, optional formula ingredients can be included to control blood glucose levels, control insulin levels and reduce homocysteine levels.

The multi-component compositions of this invention and treatment methods using them are based, at least in part, on a recognition that cancer is the result of a multi-factor etiology requiring utilization of multiple biochemical factors to successfully ameliorate or reverse conditions or symptoms of cancer. Further, the protective and therapeutic formulas of

genistein from soy isolate. Preferred compositions can further comprise components which regulate blood lipids, glucose or insulin, decrease homocysteine levels and stimulate or promote immune response or cell differentiation. Preferred compositions can further comprise components which provide cell protection from mutation and toxins.

Without wishing to be bound by any particular theory, the antioxidant components of the present formulas are believed to protect cells from damage which may lead to mutation and the generation of cancerous cells. Antioxidant components are also believed to promote restoration of healthy cells and tissue. Neovascular regulators, i.e., angiogenesis inhibitors, are believed to prevent inappropriate vascularization, help regulate growth factors to deprive cancerous cells of a blood supply and to inhibit cancer cell proliferation. Components that promote collagen synthesis are believed to also inhibit inappropriate vascularization help restore growth factors, and to generally restore or promote healthy tissue thereby inhibiting metastasis and recurrence of cancers.

Components that regulate blood lipid levels are believed to generally inhibit cancer development, growth and recurrence. Components that control blood glucose levels are also believed to generally inhibit (directly or indirectly) cancer development, growth and recurrence. Components that stimulate the immune response are believed generally to inhibit metastasis and cancer recurrence. Components that promote pH balance are believed to provide additional protection from cell damage due to oxidative stress. Components that inhibit aberrant methylation protect cells from genetic damage and inhibit carcinogenesis. Vitamins, minerals and cofactors are generally believed to improve cell and tissue health and to help maintain and/or restore normal biochemical function to cells and tissue and thereby prevent development, growth and recurrence of cancer. Nutrient components provided in the formulas herein are also believed to protect against and/or ameliorate cachexia which may result from tumor growth.

Preferred compositions of this invention combine two or more antioxidant components, two or more neovascular regulators, a component that stimulates or enhances collagen synthesis, a component that regulates blood lipid levels, a component that stimulates the body's immune response, a component that regulates blood glucose levels and mineral, vitamin and cofactor components to supplement deficiencies and help to maintain and restore normal cell biochemistry.

a complementary antioxidant strategy is employed. Different chemical types of antioxidants are combined to provide enhanced antioxidant effect. Preferred antioxidant combinations include both hydrophilic (having affinity for water or polar groups) and hydrophobic (having an affinity for lipids) antioxidants and combinations of antioxidants from different natural plant sources. In a preferred embodiment, antioxidant vitamins (vitamins C or E), the mineral zinc and potassium and different plant bioflavonoid sources are combined to achieve complementary and synergistic antioxidant effects related to cell and tissue protection and healing.

Bioflavonoids containing proanthocyanidins scavenge free radicals and chelate some minerals to prevent them from causing oxidation. These bioflavonoids are found in most plants from which they can be extracted. Commercially available proanthocyanidin-containing plant extracts include: grape seed extract (also called leucoanthocyanidin), pine bark extract (including "Pycnogenol" (Trademark, Horphag)), and bilberry extract. Ginkgo biloba and other plants which can also provide bioflavonoids, but of generally lower proanthocyanidin content, can also supplement antioxidant effect. These materials and extracts contain rather complex mixtures of catechins, tannins, oligomers and proanthocyanidins, at least some of which protect membranes from lipid peroxidation, and inhibit superoxides. They are hydrophilic antioxidants, which are many times more effective than most antioxidant nutrients at controlling free radicals, superoxides and lipid peroxides. Individual plant materials which can provide proanthocyanidins may also provide other therapeutic benefits, for example, garlic and willow bark (a source of salicylic acid) may provide additional benefit.

Oligomeric proanthocyanidins (OPCs) are polymer chains of 10 or less catechins which yield red anthocyanidin when boiled in an aqueous solution of 10% hydrochloric acid. Proanthocyanidins do not contain condensed tannins but are composed of nearly 60% catechin forms which have an extremely high affinity for collagen. Catechin binds tightly to collagen, modifies its structure by crosslinking and causes it to be resistant to enzyme degradation, such as by collagenase, or by lipid peroxidation and superoxide radicals. Proanthocyanidins inhibit capillary resistance and capillary permeability and, thus, improve vascular damage and deterioration. Collagen accumulates in vessel walls in endothelia, the connective matrix, elastin and phospholipids which helps to maintain structural integrity and protect these structures from peroxide anion damage. Plant extracts employed in this

Pine bark extract, some preparations of which are known by the trade name "Pycnogenol," is similar to leucoanthocyanidin, having relatively high OPC levels, but may possess better ability to suppress phagocytes.

Ginkgo biloba is a "middle range" proanthocyanidin possessing many of the functional characteristics of both bilberry extract and grape seed extract, but these active components are apparently present in lower concentrations. Ginkgo biloba can cause dilation of arteries, capillaries and veins and inhibit platelet aggregation. Ginkgo biloba also functions to inhibit high blood pressure and would be a preferred ingredient in formulations adapted for use by those with hypertension and related disorders.

Green tea extract, tea polyphenols, contains a small amount of 2-3% of proanthocyanidin. It nevertheless is a potent antioxidant for lipid peroxides, superoxides and hydroxyl radicals. It contains relatively high concentrations of (-) epigallocatechin gallate (EGCg), a condensed tannin polyphenol. In addition to antioxidant function, tea polyphenols also have anti-platelet, anti-cholesterolemia, anti-hypertension, anti-hyperglycemic and anti-mutagenic activities. Tea polyphenols also assist theoflavin digallate in acting as an angiotensin converting enzyme inhibitor, but do not have the undesired pro-oxidant properties of captopril.

Silymarin is an antioxidant bioflavonoid isolated from milk thistle (*Silybum marianum*). Silymarin is contains the flavonoid silybin as a major component and related compounds silydianin and silychrysin (among others) as minor components. Silymarin is typically obtained as a concentrate (80% silymarin) from milk thistle seed extract. Silymarin can also be obtained from milk thistle berries. Silymarin is reported to provide a protective effect to the liver and is believed to protect liver cells from damage due to toxins (Ferenci, P. et al. (1989) *J. Hepatol.* 9(1):105-113).

Antioxidant bioflavanoids, also include, among others, the flavanone glycosides quercitin, naringin, rutin and their aglucons, which are superoxide scavengers and inhibit oxidation of LDL. Additional antioxidant bioflavanoids include: curcumin, kaempferol, fisetin, ipriflavone, apigenein, coumadin, zingiber, malviden, galangin, robinetin, myricitin, hesperiden, taxifolin, morin, deonidin, chrysin, perlargonidin, caffeic acid any of which can be included or admixed for additional antioxidant and/or collagen-binding effect. Bioflavanoids may also be contained in plant preparations and extracts, e.g., nutgall

palmitate. Vitamin A and derivatives thereof are included in the formulas of this invention for their antioxidant function. Vitamin A function can be provided for example by retinol, retinal, retinoic acid (particularly 13-cis-retinoic acid and beta-trans-retinoic acid), and aromatic retinoids.

Tocopherols (Vitamin E, d-alpha-tocopheryl salts) are hydrophobic, lipid-based compounds with antioxidant function. They are believed to have a primary role in protecting cell membranes from lipid peroxidation. Tocopherols also scavenge free radicals in the blood and help to protect Vitamin A and selenium. D-alpha tocopherol forms, the natural forms of Vitamin E, are preferred over the less bioactive d,l-tocopherol forms. Tocopherols can be provided in a variety of forms with different counterions. D-alpha-tocopheryl acetate and gamma-tocopherol are preferred for use in the compositions of this invention. Because some subjects can exhibit a slight rise in blood pressure when Vitamin E is first taken, smaller more frequent doses or a time-released form of Vitamin E may be more appropriate for those individuals having hypertension or related conditions. Different forms or derivatives of vitamin E may exhibit distinct secondary activities, in addition to antioxidant properties. For example, vitamin E succinate has been reported to exhibit inhibition of proliferation of tumor cells (Kline et al. (1990) *Nutrition and Cancer* 14:27-41).

Lutien also called xanthophyll, a carotinoid related to beta-carotene, but not a pro-Vitamin A carotinoid, is itself a lipid peroxide scavenger and appears to promote the production of zeaxanthin, another abundant and powerful lipid-based antioxidant. Lutien is an important blood-borne carotenoid strongly related to cardiovascular health. It is found in the human retina and is believed to act, possibly in a complementary manner with zinc, to protect retinal and macular tissue from oxidative damage. Zeaxanthin, an isomer of lutein, isolated from yellow corn grits, can be employed in compositions of this invention in place of or in addition to lutien.

Beta-carotene is a lipid-based, pro-vitamin A antioxidant which quenches singlet oxygen and scavenges free radicals. It plays a role in protecting against lipid peroxidation. Beta-carotene may also have a synergistic effect with other carotenoids, including lutein or zeaxanthin, for enhanced antioxidant function. Lycopene, canthaxanthin, and apo-carotenal are other antioxidant carotenoids that are useful in the formulas herein. In preferred antioxidant combinations, two or more carotinoid antioxidants are combined.

Cartilage, an avascular tissue, is a source of angiogenesis inhibitor(s). Shark and bovine cartilage, among others, are sources of angiogenesis inhibitor and may provide collagenase inhibition as well. Chondroitin sulphate, a mucoploysaccharide found in most mammalian cartilaginous tissues and shark cartilage, is believed by many to be the most active angiogenesis regulating component of shark cartilage. The restoration of depleted chondroitin sulphates may also affect collagen stabilization which would help to normalize the collagen matrix of vascular tissue and therefore create a more stable vascular structure. Chondroitin sulphate can be provided in a number of forms with different counterions, e.g., sodium, potassium, etc. Sodium chondroitin sulphate is the form preferred for use in compositions of this invention.

Protamine sulphate is a mixture of the sulphates of basic peptides that can be prepared from the sperm or the mature testes of certain species of fish. It is an arginine rich basic protein which has been shown to be a specific inhibitor of angiogenesis, possibly due to its ability to bind to heparin. Protamine has been used in some insulin preparations to prolong the effects of insulin. Protamine is usually given as the sulphate, but the hydrochloride form may also be used.

Genistein as well as daidzein are plant-derived isoflavonoids found, for example, in soybeans, that exhibit an ability to inhibit neovascularization by controlling endothelial cell proliferation *in vitro*. Soy isolate is a natural source of genistein, daidzein or the glycoside derivatives (e.g., genistein, daidzein and sophoricoside) of these isoflavones. Soy isolate also provides nutritional benefit and may supplement depleted amino acids. Additional plant-derived isoflavonoids include kievitone. Genistein and possibly kievitone may also function as a tyrosine kinase inhibitor causing apoptosis in certain cancer cells. Certain plant derived isoflavonoids, such as genistein, exhibit estrogenic function. Such isoflavonoids can function, like estrogen, to inhibit bone loss. Phytosestrogen, particularly those isolatable from soy, can have inhibitory effects upon cancer.

Gymnema sylvestre which normalizes heparin levels is provided in the compositions of this invention, at least in part, to affect heparin levels which in turn may affect angiogenic regulation due to shark cartilage and protamine sulfate which both bind to heparin. The Gymnema sylvestre also provides for insulin/glucose stabilization which can further reduce the oxidative stress that contributes to the neovascularization factors described above.

lower toxicity. In addition, preferred forms will be generally compatible with the other components of a given mixture, will result in minimal irritation or other undesired side effects. Choices of form of a given mineral provided in a given composition of this invention will also depend on the other ingredients in the composition, particularly to avoid excessive levels of a given counter ion.

Zinc can be provided in a variety of forms and with various counter ions, including among others zinc citrate, zinc fumarate, zinc gluconate, zinc alpha-ketoglutarate, zinc lactate, zinc malate, zinc succinate, zinc picolinate or mixtures thereof. The preferred form of zinc in the compositions of this invention is zinc (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs Cycle) i.e., a mixture of the zinc salts of citric, fumaric, malic, alpha-ketoglutaric and succinic acids. Zinc may have an indirect effect on bone resorption by inhibiting cadmium accumulation.

Chromium can be provided by a variety of dietary sources including, among others, brewer's yeast, liver, potatoes with skin, beef, fresh vegetables and cheese. Chromium exists in a dinicotino-glutathionine complex in natural foods. Such dietary and natural materials can provide sources of chromium for use in compositions of this invention. As with other minerals, there are generally a variety of forms of chromium that are useful in the compositions of this invention including, for example, chromium sulphate. Chromium nicotinate (Chromium-nicotinic acid complex) is a preferred form of chromium for use in the formulas of this invention. Chromium picolinate can be employed in the formulas of this invention, but is not generally preferred. Chromium enhances insulin activity and as a result can affect blood lipids. For example, chromium nicotinate acid complexes can lower blood triglyceride levels. Chromium also decreases calcium excretion.

Magnesium can be provided in a variety of forms and with various counter ions, including among others magnesium citrate, magnesium fumarate, magnesium gluconate, magnesium alpha-ketoglutarate, magnesium lactate, magnesium malate, magnesium succinate, magnesium picolinate, magnesium sulphate or mixtures thereof. Preferred forms of magnesium in the compositions of this invention are magnesium citrate, magnesium malate, magnesium malate-citrate, and magnesium (Krebs) in which the counter ions are a mixture of the anions of the five primary organic acids of the tricarboxylic acid cycle (Krebs

composition. These ranges can be readily adjusted by those of ordinary skill in the art of nutrient and therapeutic formulation to other forms of the minerals noted above.

A mineral complex can optionally be combined with the compositions of this invention in addition to or substituted for specific minerals in the various formulas. Preferably, the mineral complex is used to supplement nutritional minerals not already included in specific formulation. A preferred mineral complex includes absorbable salt or chelated forms of:

major mineral components: calcium, magnesium, and potassium also chloride (e.g., as potassium chloride) and sulphate (e.g., as manganese sulphate);

intermediate level components: zinc, manganese,.boron and copper;

minor components: chromium, selenium, iodine, molybdenum, vanadium, lithium, rubidium, silicon (as silica), nickel, phosphorus, strontium and cadmium;

trace minerals: preferably from natural sources e.g., marine organic minerals or sea water concentrate.

The minerals may be provided in a variety of salt and complex forms, i.e., as the salts of Krebs cycle acid anions: aspartate, citrate, fumarate, malate and/or succinate salts; as salts of amino acids (e.g., arginates); as picolinate salts; as ascorbate salts, as nicotinate salts. Silicon is preferably provided as the trisillicate anion, e.g., magnesium trisillicate. Selenium is preferably provided as organoselenium compound, e.g., selenomethionine. A variety of natural sources of minerals are known to the art including plant extracts, and can be used to provide minerals in the formula of this invention. A preferred mineral complex provided in Table 1.

Minerals specifically included in a given formulation of this invention are preferably provided at the level indicated in that formulation. For an individual diagnosed with a particular mineral deficiency (e.g., iron deficiency), dosages of a given mineral may be increased as needed and additional minerals, e.g., iron, may be added to the mineral complex.

general nutritional supplementation as well as antioxidant function, as discussed above. Vitamin B6, i.e., pyridoxine, vitamin B12, i.e., cobalamine, and folic acid (folate) provide general nutritional supplementation, and more specific benefits. Folate and vitamins B6 and B12 have antianemia properties. Folic acid decreases homocysteine levels. Vitamin B2, i.e., riboflavin, provides general nutritional supplementation. Vitamin B6 deficiency may detrimentally effect bone formation. Vitamin D can provide positive beneficial effect in protection and/or inhibition of cancer. A preferred form of vitamin D is vitamin D3.

A vitamin B complex can be employed in addition to or substituted for Vitamin B components of the formulas of this invention. A preferred Vitamin B complex includes:

Vitamin B1 (thiamine)	10μg - 100 mg	(10%))
Vitamin B2 (riboflavin)	10μg - 50 mg	(5%)
Vitamin B3 (nicotinamide or niacinamide, preferably as niacinamide ascorbate)	1 mg-1,000 mg	(53%)
Vitamin B5 (pantothenic acid)	1 mg -200 mg	(26%)
Vitamin B6 (pyridoxine HCl)	10μg - 3 mg	(5%)
Vitamin B12 (cyanocobalamin)	1μg - 200 μg	(0.03%),

where a preferred range and preferred specific relative amounts of the components are given.

Amino Acids

The formulas of this invention include amino acids that have a particular therapeutic function. Formulas of this invention may also contain additional amino acids for nutrient supplementation or for compensation for an individual's deficiency. Compositions of this invention can include any of the following: alanine, arginine, aspartic acid, cystine, glutamic acid, glycine, histidine, isoleucine, leucine, lysine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, carnitive (all in the biologically active L-form) and gamma aminobutyric acid. When present in a given formula, a specifically listed amino acid is preferably provided in the amount needed to provide the desired therapeutic effect. Additional nutritional amino acids are preferably provided in an nutritionally effective amount.

(d-limonene), narigninen, tangeritin, nobelitin, iberene and d-carcone are exemplary monoterpenes. D-limonene is a preferred monoterpene for use in the formulas of this invention.

Source of omega-3-fatty acids

Omega-3 oils are a family of oils having relatively high concentrations of omega-3 polyunsaturated fatty acids, including eicosapentaenoic acid (EPA) and alpha-linolenic acid. These oils exhibit a hypolipidaemic action, especially a reduction in plasma triglycerides linked to a reduction in very-low density lipoproteins (VLDL). They also exhibit anti-inflammatory effects. Fish oils and other marine oils typically contain high levels of omega-3-fatty acids. In general, omega-3-fatty acids are believed to reduce blood pressure, and lower cholesterol and triglyceride levels. Omega-3 fatty acids are found in a variety of naturally-occurring sources and may be provided in their acid form or as fatty acid salts or fatty acid esters.

Chronic omega-3-fatty acid deficiency correlates with chronic nephropathic injury. EPA and DHA (docosahexanoic acid) produce an anti-inflammatory effect by reducing prostaglandin production and displacing arachidonic acid. HDL, triglycerides and fibrinogen have also been successfully reduced by omega-3-oils. Omega-3-fatty acids are included in formulas herein, at least in part, for their function in the control of blood lipid levels.

Flaxseed (also called Linseed) is a nutrient rich in omega-3-fatty acids. It is a major source of alpha-linolenic acid (an omega-3-fatty acid) and lignin. Ground flaxseed is a preferred source of omega-3-fatty acids over fish oils for use in compositions of this invention. The use of flaxseed oils, particularly in cases where the formula is being used chronically for protective or prevention benefit, avoids the potential toxicity that has been associated with long term use of fish oils. Fish and marine oils or individual omega-3-fatty acids, including EPA, and ALA (and their analogous fatty acid esters) can be used in these formulations in place of flaxseed. Omega-3 fatty acids may have a protective effect against tumorogenesis.

Essential fatty acids (EFAs) are those fatty acids that cannot be made by the body and must be supplied through the diet. Fresh, poly-unsaturated vegetable oils are a major source for EFAs (linoleic, linolenic and appropriate levels of arachidonic acids). EFAs have a variety of beneficial effects including reduction of blood pressure, lower cholesterol, and lower triglyceride levels. Linolenic acid is one essential fatty acid for formulations of this

form for this invention. Carnitive can be also be provided as the l- or d,l-form as hydrochloride or other salts.

Sesamin/Sesamolin are constituents of sesame oil and/or sesame seeds. These components are believed to affect blood lipid levels.

Phytosterols, including plant sterols, which comprise beta-sitosterol, campesterol, and/or stigmasterol have been shown to reduce the absorption of the LDL cholesterol component of foods in the gut on a dose dependent basis of approximately one-to-one sterols to cholesterol, while enhancing beneficial HDL to positively effect the LDL-HDL Ratio. Plant sterols have been shown to primarily block harmful LDL cholesterol and admit beneficial HDL cholesterol, the levels of which can actually be elevated. Plant sterols can be provided in the formulas of this invention in soy oil or by addition of individual sterol components. A commercially available mixture of phytosterols, "Cholestatin III" (about 62% beta-sitosterol, about 24% campesterol and about 14% stigmasterol), produced in bacterial fermentation, is preferred for use in the formulas of this invention. Saw palmetto is another useful source of phytosterols.

Gymnema sylvestre

Gymnemic acid, the active ingredient in gymnema sylvestre, suppresses sensitivity to sugar and its absorption, thereby reducing blood glucose levels. It also restores the levels of three chondroitin sulfates which may assist in collagen repair and/or aid in angiogenesis regulation. Heparin sulphate levels are increased in diabetics while three chondroitin sulfates are decreased. Gymnema sylvestre which normalizes heparin levels could play a supporting role in the angiogenic regulation of other ingredients in this formulation, namely shark cartilage and protamine sulfate. Both are angiogenic regulators which bind to heparin. The restoration of depleted chondroitin sulfates probably plays a role in collagen stabilization which would help to normalize the collagen matrix and therefore create a more stable structure upon which angiogenesis regulation could more easily exist. The insulin/glucose stabilization effects of Gymnema sylvestre would reduce the oxidative stress that contributes to the neovascularization factors described above.

Garlic/Garlic Extract

Alicin and garlicin are active ingredients of garlic and garlic preparations that have been associated with control of blood glucose levels, cholesterol reduction and triglyceride reduction. These materials are included in the formulas herein for their general inhibitory

formulas of this invention as a calcium regulator that is a factor for promotion of collagen synthesis and more importantly for its additional function in stimulating or enhancing immune response. Vitamin D3, preferably 22-oxa-vitamin D3, is also provided in osteoporosis formulas herein.

Vitamin K

Vitamin K is a cofactor involved in blood coagulation. Vitamin K1, or phylloquinone, is a preferred form of Vitamin K for use in the formulas herein. Vitamin K is also reported to increase calcium binding affinity of certain proteins in bone formation. Vitamin K is included in formulas of this invention to supplement any vitamin or cofactor deficiency and for its calcium-binding function which indicates usefulness in tissue regeneration and benefit for osteoporosis.

Melatonin, a hormone, provides for inhibition of prolactin which is a stimulator of growth of breast cancer cells. Melatonin thus provides indirect inhibition of cancer cells.

Betaine HCl, Pepsin and Sodium Bicarbonate

Inappropriate acidity is believed to be a factor in the pathogenesis of chronic disease. Mitochondrial antagonism resulting in oxidative stress is a probable mechanism. Betaine HCl, pepsin and sodium bicarbonate have all demonstrated the ability to help regulate hyperacidity. In addition, betaine HCl and pepsin are among digestive enzymes often deficient in the elderly as well as chronic disease sufferers. Betaine may also effect methionine metabolism to provide protection from DNA damage due to aberrant methylation. Inappropriate acidity may result in bone dissolution. Factors that control acidity can provide benefit in osteoporosis and are included in osteoporosis formulas herein.

Specific cancer preventative and therapeutic formulas of this invention include:

1. Formula I which comprises:
   - (i) antioxidants selected from:
     - (a) a plant extract having antioxidant effect comprising bioflavanoids, particularly an extract providing a major source of proanthocyanidins, such as bilberry extract, grape seed extract, or pine bark extract. Bioflavanoids of lower proanthocyanidin content, for example, ginkgo biloba, can also be used to supplement major sources; combinations of plant materials and extracts can also be employed;

(ix) a source of omega-3 fatty acids, particularly conjugated dienoic fatty acids, e.g., linoleic acid (ALA) and/or enosapentaenoic acid (EPA), a preferred source is ground flax seed;.

4. Formula IV which comprises:
The components of Formula III; and
protamine sulphate and/or glucosamine sulphate (a preferred glycosaminoglycan and source of glycosamine, a building block for collagen synthesis);
vitamin D3, preferably derivatives thereof which induce little or substantially no hypercalcification (e.g., 22-oxa-vitamin D3); and
branched amino acids.

5. Formula V which comprises:
The components of Formula IV and
quercitin;
Saw palmetto;
vitamin B12 and folic acid (or optionally vitamin B-complex);
absorbable potassium and selenium;
alpha-lipoic acid (also called thiotic acid); and
allicin (or garlic extract);.
Formula 5A which comprises the components of Formula 5 where the antioxidant carotenoids are a mixture of beta-carotene and lutein.
Formula 5B which comprises the components of Formula 5 which contains a mixture of chondroitin sulphate, protamine sulphate and shark cartilage and where the antioxidant carotenoids are a mixture of beta-carotene and lutein.

6. Formula VI which comprises:
The components of Formula V, 5A or 5B and
silymarin;
curcumin;
niacinamide;
a source of essential fatty acids, particularly conjugated dienoic fatty acids; for example, linoleic acid and
one or more of sodium bicarbonate, betaine HCl or pepsin.

The components of Formulas VIII, 8A or 8B and
cinnamon extract;
absorbable copper;
indole-3-carbinol;
fenugreek seed (preferably defatted powder);
N-acetylcysteine;
pectin, e.g., citrus or apple pectin;
betaine HCl and pepsin.

Formula 9A comprises the components of Formula IX containing a mixture of monoterpenes: limonene, naringenin, tangeritin and nobelitin.

10. Formula X which comprises:
The components of Formula IX or 9A and
coumarin;
zingiber;
ginger;
absorbable boron;
vitamin K1;
sesamolin; and
methionine.

Formula 10A comprises the components of Formula X and contains a mixture of monoterpenes including limonene, naringinen, tangeritin, nobiletin, and iberene.

Formula 10B comprises the components of Formula X wherein the source of omega-3 fatty acids is a fish oil.

11. Formula XI which comprises:
The components of Formula X, 10A or 10B and
nutgall; malviden; galangin; robinetin; myricitin;
absorbable manganese;
alpha-linoleic acid; and
lysine.

Specific formulas for the treatment of female cancers include:

14. Formula XIV which comprises:

(i) Antioxidants:

A source of proanthocyanidins and/or bioflavanoids (e.g., pine bark extract, bilberry extract, etc.);

A neovascular regulator (e.g., genistein, cartilage, etc.);

vitamin C;

vitamin E;

vitamin A;

beta-carotene;

(ii) Vitamin D3; and

(iii) calcium.

15. Formula XV which comprises the components of formula XIV and

selenium;

folic acid;

omega-3/omega-6 fatty acids (flax seeds or fish oil); and

soy isolate containing phytoestrogens and/ or phytosterols (phytoestrogens can be replaced with soy isoflavones, such as genistein or daidzein).

16. Formula XVI which comprises the components of formula XV and

melatonin;

lycopene; and

shark or bovine cartilage.

17. Formula XVII which comprises the components of formula XVI and

limonene;

arginine; and

conjugated dienoic linoleic acid.

18. Formula XVIII which comprises the components of formula XVII and

curcumin;

niacin; and

naringenin.

Creatine phosphate and eugenol have antioxidant activity and can be employed in formulas of this invention to provide additional protection against oxidative stress and cell damage.

Phosphatidylcholine, particularly polyunsaturated phosphalidyl choline, can be added to any of the formulas herein to provide control of the blood lipid levels.

All of the above specific formulas can be combined with cellular antioxidants including glutathione peroxidase, superoxide dismutase and/or catalayze. All of the above specific formulas can be combined with fruit and/or grain fiber.

All of the above formulas can be combined with taxol, or structurally related anticancer agents as well as Juniper yew extract with the proviso that these materials can exhibit significant toxic effect. Similarly, the formulas of this invention can be combined with mistletoe extract again with the proviso that this material can exhibit toxic effect.

The formulas of this invention can optionally include nutrients, vitamins and minerals other than those specifically listed to supplement particular nutritional deficiencies of given individuals, for example, chromium, iron, or other mineral may be provided or its concentration increased to supplement a given deficiency. Similarly, a particular vitamin or amino acid deficiency can be supplemented. Analogously, a given formulation can be adapted for sensitivities or allergies of a given individual.

Specific components listed in Table 2 and in the Formulas herein which are natural isolates can be replaced or supplemented with extracts and/or powders (seeds, etc.) derived from the natural source of the component.

A number of the components of formulas herein can be obtained from natural sources. Isolated major active ingredients can be recombined with extract obtained from the natural source to provide minor components that may enhance function of the major ingredient, e.g., purified genistein can be combined with soybean extract for enhanced effect.

The formulas of this invention an also be combined with enzymes such as papain and bromelaine to aid digestion.

TABLE 2 (CONTINUED)		
N-acetyl-L-cysteine	1, 4, 6, 7, 10	5 - 3,000 mg
L-cysteine	1, 6, 7, 10	1 - 2,000 mg
Glutathione	1	1 - 1,000 mg
CoQ10	1, 6	4 - 400 mg
Chondroitin Sulfate	2, 3	10 - 10,000 mg
Glucosamine Sulfate	2, 3	10 - 10,000 mg
Soy Isolate (e.g., genistein and other plant isoflavones)	2, 3	50 - 1,500 mg
Protamine Sulphate	2, 3, 9	10 - 900 mg
Cartilage (bovine)	2, 3	1 - 30,000 mg
Cartilage (shark)	2, 3	1 - 1,499 mg
Vitamin B5 (pantothentic)	6	1 - 200 mg
Vitamin B1 (thiamine)	6	10 µg - 100 mg
Folic Acid	6, 10	100 µg-1,500mg
Vitamin B2 (Riboflavin)	6	1 µg - 50 mg
Vitamin B6 (Pyridoxine HCl)	6, 10	1 µg - 200 mg
Vitamin B12 (Cyanocobalamin 1%)	6, 10	1 µg - 100 mg
Nicotinamide (Vitamin B3, nicotinamide ascorbate)	6	1 - 500 mg
B complex†	6, 10	1 - 500 mg
Calcium (Krebs)	4, 6, 11	10 -10,000 mg
Zinc (Krebs)	1, 6, 9	10 - 3,000 mg
Magnesium (Krebs)	6, 9	3 - 10,000 mg
Chromium nicotinate	1, 4, 6, 9	2 µg - 50 mg
Selenium (1-selenomethionine)	1, 6, 11	1 µg - 50 mg
Potassium citrate	1, 6	30 - 18,000 mg
Strontium	6	1 µg - 800 mg
Copper (cupric sulfate)	6, 11	1 µg - 500 mg
Manganese (Krebs)	3, 6	10 µg - 100 mg
Silicon (magnesium trisillicate)	6	10 µg - 200 mg

TABLE 2 (CONTINUED)		
L-methionine	6, 7	10 - 300 mg
Branched Chain Amino Acids*	3, 6	10 - 70,000 mg
Betain HCl	5, 6	1 - 10,000 mg
Pepsin	5, 6	1 - 10,000 mg
Sodium Bicarbonate	5, 6	1 - 10,000 mg

† B complex = Vit. B1, Vit. B2, Vit. B3, Vit. B5, Vit. B6, and Vit. B12.
*Branched Chain Amino Acids = L-leucine, L-isoleucine, and L-valine.

Table 2 provides a summary of certain biochemical functions of components that are useful in cancer-protective and cancer-therapeutic formulas of this invention. A single component may provide more than one of the listed biological functions in a given composition. Table 2 provides a list of exemplary components of the formulas of this invention providing a preferred range of amounts of individual components that can be combined in the formulas of this invention. The amounts listed in Table 2 are average daily adult dosages. Biological functions associated with osteoporosis are not listed.

As listed in Table 2, the cancer-preventative and therapeutic formulas of this invention comprise components that (1) have antioxidant function to control oxidative stress and prevent cell damage, (2) promote and/ or stimulate collagen synthesis to provide healthy tissue and inhibit metastasis and recurrence, are (3) neovascular regulators which control angiogenesis and function to limit blood supply to cancers, (4) regulate blood lipid, particularly lipoprotein (a), levels, (5) decrease cell/tissue acidity and promote pH balance, (6) supplement dietary deficiencies, non-absorption, cachexia or nutrient spillage, (7) inhibit or prevent aberrant methylation, (8) stimulate or enhance immune response or cell differentiation, (9) control blood glucose levels, (10) lower homocysteine levels or (11) have other antitumor or anticancer activity.

One or more of the functionalities listed in Table 2 can be provided in the compositions of this invention by art-known equivalents including equivalents from natural sources and/or drug equivalents.

Compositions of this invention can be provided in a variety of nutrient and dosage forms including pills, tablets, capsules, lozenges, powders, solutions, suspensions, injection dosage forms and the like. Compositions of this invention can be administered to individuals orally, intravenously, and by various forms of injection and various forms of absorption (e.g., dermal, sublingual). Active ingredients of the formulas of this invention can be combined with excipients, fillers, buffering agents and the like to prepare desired dosage forms. Generally preferred dosage forms are those appropriate for oral administration. In cases of use for cancer therapy, the optimum mode of administration can depend upon the type of cancer.

The formulas of this invention that are useful in the treatment and prevention of the various disease conditions discussed above combine a number of related ingredients. The therapeutic and preventative compositions of this invention are based at least in part on the

and to match individual needs or problems of a given patient by those of ordinary skill in the art.

U.S. Patent application 08/018,273, filed February 4, 1998, which is incorporated in its entirety by reference herein relates to nutrient and therapeutic formulations for treatment of cardiovascular disease and the complications of diabetes. The formulas therein combine antioxidants, neovascular regulators and other components having particular benefits for cardiovascular disease and diabetes complications. This patent application provides exemplary formulations including certain of the components herein and provides additional guidance for appropriate dosage. Formulas of this invention can be adapted for treatment of diabetics having cancer using components and dosages provided in this U.S. application.

Table 2 provides a summary of the general biological functions of most components that are believed to be beneficial for the treatment of cancer. This listing provides the inventor's current understanding of the functions provided by components included in the preferred composition and provides guidance for the choice of alternative components with similar functionality. The inventor, however, does not wish to be bound by the specific functional correlations listed in these tables or by proposed functionality of individual activity. The etiology of the diseases and conditions discussed herein is complex and a given component of a formula of this invention may have several different effects. In some cases, the component listed in the table is itself a mixture, for example, pine bark extract is a combination of naturally occurring compounds. In these cases, different components of the listed mixtures may contribute to different functions listed in Table 2.

The compositions of this invention specifically ameliorate cancer. The diagnosis and symptoms of various cancer conditions are understood in the medical arts and a variety of methods are known in the art to evaluate the severity and extent of the conditions.

Exemplary sources of certain components of the formulas herein are as follows: The following are sources of ingredients listed in Table 2:

Bilberry extract, as a dry hydroalcohol extract containing anthocyanosides corresponding to 25% (by weight)of anthocyanidines obtained from Indena (Milan, Italy). Grape Seed Extract (Leucocyanidins) (90-100% OPCs) can be obtained from Indena (Milan, Italy).

Pine Bark Extract (OPC 90%) can be obtained from Euromed (Barcelona, Spain).

reported to typically contain (in mg/g protein) 0.15 to 0.72 mg daidzein, 0.48 to 1.51 mg genistein, 0.05 to 0.26 glycitein with a total isoflavone content of 0.68 to 2.49 mg (aglucone units adjusted for molecular weight).

Phytosterol complex, "Cholestatin III" can be obtained from several sources.

Vitamin E, d-alpha-tocopheryl acetate (natural source, powder) can be obtained from B&D Nutritional Ingredients, Inc. (Carlsbad, CA).

Flax seed powder containing about 23 mg of alpha-linolenic acid (omega-3-fatty acid) per 100 grams powder can be obtained from Honeyville Grain Inc. (Salt Lake City, UT).

Fenugreek seed powder can be obtained from Botanicals International (Long Beach, CA).

Ginkgo biloba L. powder extract about 26% flavonglycosides and Gymnema sylvestre powder can be obtained from Motherland International Inc. (Chino, CA).

Other components listed in Table 2 can be obtained from a variety of commercial sources.

Those of ordinary skill in the art of formulation of nutrients and therapeutic compositions will appreciate that components functionally equivalent to those specifically disclosed herein, as well as alternative forms and sources in addition to those specifically disclosed herein for individual composition ingredients are available. This invention is intended to encompass all such functional equivalents and alternatives that are readily known to the art.

(a) antioxidant components

a plant extract having antioxidant effect;

an antioxidant carotinoid;

an antioxidant flavonoid;

Vitamin C;

Vitamin E; and

Vitamin A

said antioxidant components in a combined amount effective for providing an antioxidant effect and/or for stimulating collagen synthesis;

(b) neovascular regulators and/or factors for collagen synthesis:

chondroitin sulphate, and

genistein

in a combined amount effective for neovascular regulation and/or stimulating collagen synthesis;

(c) minerals:

absorbable zinc;

absorbable chromium;

absorbable magnesium; and

absorbable calcium; and

(d) L-arginine and branched amino acids

each present in an amount effective for compensating for nutritional deficiency.

9. The composition of claim 8 further comprising:

Gymnema sylvestre; Saw palmetto; Fenugreek; Ginkgo biloba; silymarin; quercitin or a mixture thereof each present in an amount effective for providing therapeutic and/or protective function.

10. The composition of claim 1 further comprising 22-oxa-vitamin D3.

11. The composition of claim 1 further comprising a composition effective for treatment of osteoporosis selected from the group of formulas Osteo I-Osteo-V.

12. The composition of claim 1 further comprising a therapeutically effective amount of sulforaphane.

absorbable boron.

18. A method for treating and/or preventing a symptom condition or disorder associated with cancer in an individual having cancer which comprises the step of administering to said individual the composition of claim 1.

19. A method for treating and/or preventing a symptom condition or disorder associated with cancer in an individual having cancer which comprises the step of administering to said individual the composition of claim 11.

20. A method for treating and/or preventing a symptom, condition or disorder associated with in an individual having osteoporosis which comprises the step of administering to said individual the composition of claim 15.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17633

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, P ----- Y, P	US 5,895,652 A (GIAMPAPA) 20 April 1999, see entire document.	1, 3, 18 ------- 2, 4-17, 19 20
Y, P	US 5,840,715 A (FLORIO) 24 November 1998, see entire document.	1-20
Y	US 5,536,506 A (MAJEED et al) 16 July 1996, see entire document.	1-20